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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,816	03/27/2002	Michael Valentine Agrez	SW-046 XX	9944

207 7590 12/02/2005

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 12/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,816	AGREZ ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *217-221,225,238,242-245,247,249,252-254 and 264-274* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *217-221,225,238,242-245,247,249,252-254 and 264-274* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *Sept 30, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 223, 224, 236, 237, 240, 241, 246, 248, 250, 251 and 255-263 have been canceled. Claims 217-221, 225, 238, 242-245, 247, 249, 252-254 have been amended. Claims 264-274 have been added. Claims 217-221, 225, 238, 242-245, 247, 249, 252-254 and 264-274 are pending and under consideration.

Sections of Title 35, U.S. Code not found in this action, can be found in a prior action.

It is noted that support for the binding of Beta6 to ERK2 or JNK-1 can be found on pages 28-33; support for the binding of ERK2 to beta3 and beta5 can be found on page 34, lines 4-5.

Claims 217-221, 225, 238, 242-245, 247, 249, 252-254 and 264-274 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting the growth of a cancer cell ex vivo or in vitro comprising contacting said cell with a polypeptide fragment of the domain of beta6, 3 or 5, responsible for the direct interaction with ERK2, or contacting the polypeptide fragment of the domain of beta6 responsible for the direct interaction with JNK-1, does not reasonably provide enablement for the disruption of the binding of ERK2 or JNK1 to any other beta integrin subunit, or the disruption of the binding of any other ERK or JNK MAP kinase to the genus of beta integrins by "agents" other than the aforesaid fragments of the cytoplasmic domain of beta3, beta5 or beta6 or the peptides of SEQ ID NO:2, 2, 22 and 23, or the inhibition or prophylaxis of cancer within a patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

(A) as drawn to the prophylaxis of cancer

Claim 247 and new claim 266 now requires that the method be for prophylaxis of cancer. In order to carry out the claimed method for prophylaxis, it would be necessary to know which individuals are going to develop cancer, the location of said cancer, the time at which the cancer would develop and the length of time before said development of the cancer at which the instant methods should commence. The specification fails to address any of these issues, thus one of

skill in the art would be subject to undue experimentation without reasonable expectation of success in order to ;practice the claimed methods for the prophylaxis of cancer.

(B)As drawn to the treatment of cancer in vivo

Further, the claims encompass a method of treating an individual having a cancer comprising administering polypeptide sequences. The art recognizes general problems with the administration of protein drugs, namely short half-life in vivo, necessitating multiple administrations (Johnson and Tracey, 'Peptide and Protein Drug Delivery', In: Encyclopedia of Controlled Drug Delivery, Vol. 2, 1999, pages 816-833). The art teaches that "major stability, release and manufacturing challenges" (page 816, second column, lines 1-5) must be met in order to overcome the technical difficulties associated with the delivery of proteins in vivo. The specification does not teach a means for the delivery of the polypeptide agents to the appropriate site and the efficacious uptake by the tumor to result in the inhibition of cancer cells in a patient. Therefore it would be undue experimentation in order for one of skill in the art to determine the required dosage for the required length of time, and the means to stabilize and then release said polypeptides in vivo using techniques which preserve the ability of said polypeptides to function as claimed.

(C)As drawn to the direct interaction between the JNK or ERK MAP kinase families and integrin beta subunits

The claims are broadly drawn to methods which encompass any integrin beta subunit. It is noted that the priority document filed 28 June 1999 states that although no MAP kinase or any other subunit form of MAP kinase has been shown to bind to any of the 23 known integrins, the inventors have surprising determined that MAP kinase binds directly to the cytoplasmic domain of alpha-v-beta6 (page 2, lines 14-17). Thus it would be undue experimentation, without reasonable expectation of success to practice the broadly claimed methods which encompass any integrin beta subunit, because the prior document actually teaches away from using the method directed to the interaction between ERK2 and the beta subunits which are not beta3, 5 and 6 subunits, or the interaction with JNK-1 with beta subunits which are not beta6. The art recognizes that MAP kinases comprising three different families: the ERK, JNK and p38, and that individual members participate in different signaling cascades (Garington and Johnson, Current Opinion in Cell Biology, 1999, Vol. 11, pp. 211-218, reference of the IDS filed July 30,

2002, page 212, figure 1) and are regulated by different scaffolding proteins (ibid, page 213, figure 2). Because MAP kinases such as ERK3-5 and p38 are present in entirely different signaling cascades and are bound by different scaffolding proteins such as MP-1 which binds to ERK1 and JIP-1 or MEKK1 both of which lead to enhanced JNK activation, one of skill in the art would reasonably conclude that the binding of ERK1 or JNK directly to the cytoplasmic domain of beta6 did not provide a nexus for the binding of any MAP kinase directly to beta6 or any other integrin beta subunit because the MAP kinases differ in protein-protein interactions with other known members in signaling cascades as exemplified by figure 2 of Garington and Johnson. Given the lack of objective evidence in the specification for the direct binding MAP kinases which were not ERK2 or JNK-1 to an integrin beta subunit which was beta6 or any other integrin, one of skill in the art would be subject to undue experimentation in order to practice the broadly claimed method

(D)As drawn to agents which are not fragments of the cytoplasmic domain of alpha-v-beta6, or the peptides of SEQ ID NO:2, 2, 22 and 23.

Claims 217, 219-221, 225, 238, 242, 243, 245, 247, 249, 252-254, 265, 266-274 are drawn to methods reliant on the identity of an agent, which comprises a "polypeptide sufficiently homologous" with the binding domain of a map kinase to bind to said map kinase. The specification teaches agents which comprise the integrin-map kinase binding domain and the peptides of SEQ ID NO:2, 3, 22 and 23. When given the broadest reasonable interpretation the term "agent" is not limited in scope to molecules comprising the disclosed fragments of the integrin cytoplasmic regions which binds to ERK2 or JNK-1 or to antibodies which bind to said cytoplasmic regions or the binding regions of ERK2 and JNK-1 that interact with the cytoplasmic domain of alpha-v-beta6. The specification does not provide teachings of how to make this genus of homologous polypeptides on which the instant method claims depend. The specification has not taught how to make the sufficiently homologous polypeptides which would function as claimed.

Given the lack of teachings in the specification regarding methods reliant on MAP kinases beyond those or EKR2 and JNK, the negative teachings of the priority document regarding the binding of JNK-1 to integrin subunits other than beta6, or the binding or ERK2 to integrin subunits other than beta3, 5 or 6, and the lack of teachings in the specification regarding

the making of the required sufficiently homologous polypeptides, one of skill in the art would be subject to undue experimentation in order to practice the broadly claimed methods.

Applicant argues that since the time of filing it has been further demonstrated that ERK2 can bind to beta2, and therefore this clearly shows that MAP kinase binding is not restricted to the beta6 subunit. This has been considered and found partially persuasive. While not limited to the beta6 subunit, the evidence provides no nexus for the binding of ERK2 or JNK-1 to any other beta integrin subunits other than beta3, beta5 or beta6. Applicant contends that this relationship is also not limited only to ERK2. Again, the binding of ERK2 to beta3, beta5 or beta6 and the binding of JNK-1 to beta6 does not provide a nexus for the binding of any other MAP kinase in the JNK or ERK families to bind to beta3, beta5, beta6, or any other beta subunit in cancer cells.

Applicant argues that those of skill in the art would be able to readily practice the invention as claimed because of the disclosure of an ELISA protocol for detection of MAP kinase-integrin binding, wherein agents can be screened for antagonism to said binding. This has been considered but not found persuasive. Because the specification has identified only a limited number of agents which are fragments of the beta subunits involved in the interaction between ERK2 and beta3, 5 or 6 or the peptides of SEQ ID NO:2, 2, 22 and 23, there is no reasonable expectation that other interactions exist between beta subunits and other members of the ERK and JNK families in cancer cells.

With regard to the limitation of an agent which is a polypeptide moiety sufficiently homologous with the binding domain to bind to the MAP kinase, it is noted that the claims are now specifically drawn to a method of inhibiting the growth of a cancer cell. In order for the method to be operative, it would be necessary that the "sufficiently homologous polypeptide" be able to compete with the MAP kinase in a cancer cell. The requirement of 112, first paragraph, is that one of skill in the art be able to make and use the invention without undue experimentation and with reasonable expectation of success. The specification does not teach how to make such a "sufficiently homologous peptide" which would function as claimed. Applicant contention that polypeptides could be screened for the ability of disrupting MAP kinase-integrin binding would constitute undue experimentation because it would require that

one of skill in the art search for and verify the activity of said variant polypeptides before they could be used in the instant method of inhibiting growth of a cancer cell.

Applicant argues that because they were the first to discover the relationship between integrins and MAP kinase they deserve a broad scope of protection over their invention. This has been considered but not found persuasive. The scope of the claims must be commensurate with the scope of the enablement set forth, and there is not objective evidence hat cancer could be treated by polypeptides sufficiently homologous to a ERK family member or a JNK family member.

Given the lack of teachings on all of the above, one of skill in the art would be subject to undue experimentation in order to make and use the instant invention.

Claims 217, 219-221, 225, 238, 242, 245, 247, 249, 252, 253, 254, 265-274 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 217, 219-221, 225, 238, 242, 247, 249, 252, 253, 254, 266, 267, 269-274 are method claims dependent upon the identity of a polypeptide moiety sufficiently homologous with the binding domain of a beta integrin subunit to bind to a JNK or ERK MAP kinase. Thus the claims are reliant upon a genus if polypeptides which vary in structure from the binding domain of the beta integrin subunit. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written

description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id. In the instant claims, the polypeptides sufficiently homologous to the binding domain of a beta integrin subunit which can bind to a JNK or ERK MAP kinase is the naming of a type of material, but does not constitute an adequate description of said material.

The specification discloses the polypeptides of SEQ ID NO:2, 3, 22 and 23 which antagonize the binding to beta6. This disclosure fails to adequately describe the claimed genus which tolerates numerous structural deviations from SEQ ID NO: 2, 3, 22 and 23 and antagonize the binding to beta integrin subunits other than beta6.

Because the products on which a method claim is based are not adequately described, the method itself is not adequately described.

All other rejections and objections as stated in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
11/28/2005